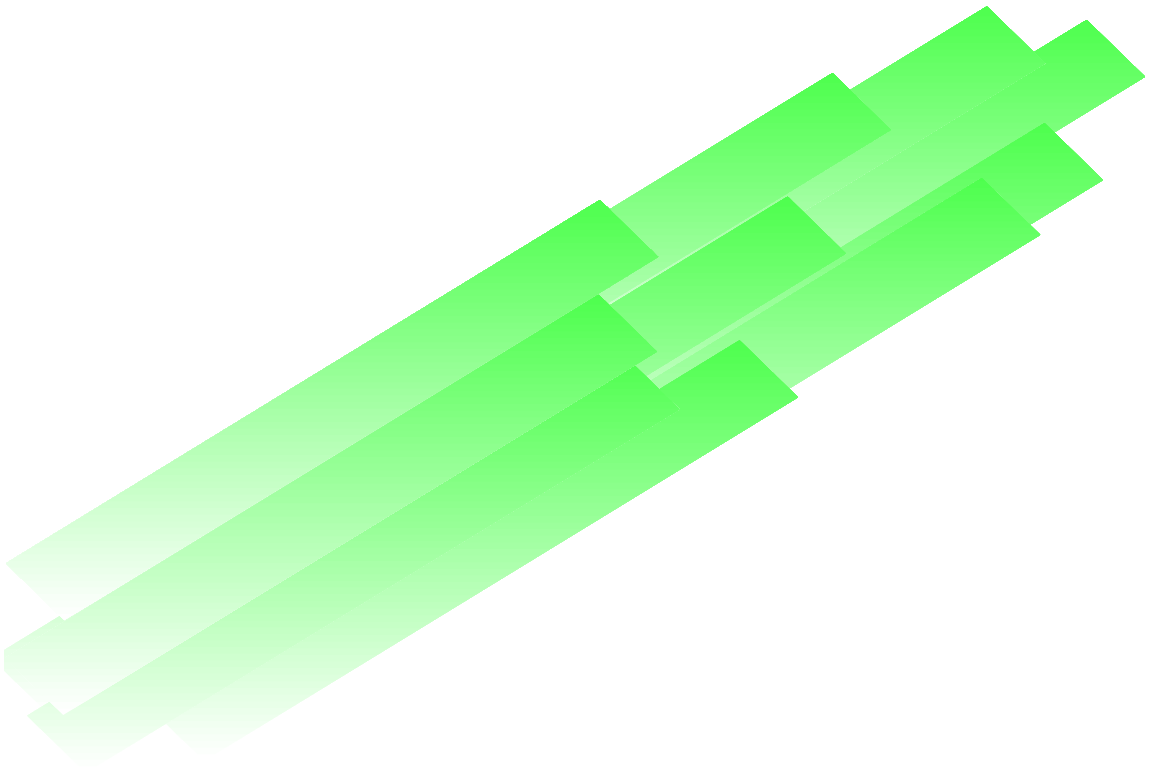
Guidance for Industry

Labeling Guidance for Venlafaxine Hydrochloride Tablets



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (Effexor®; Wyeth-Ayerst; 20-151/S-005; Approved June 25, 1996). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

II. LABELING

VENLAFAXINE HYDROCHLORIDE TABLETS

DESCRIPTION

Venlafaxine hydrochloride is a structurally novel antidepressant for oral administration. It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated (±)-1-[∝-[(Dimethylamino)methyl]-*p*-methoxybenzyl]cyclohexanol hydrochloride and has the molecular formula of $C_{17}H_{27}NO_2 \cdot HCl$. Its molecular weight is 313.87. The structural formula is shown below.

[*INSERT STRUCTURAL FORMULA HERE*]

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[1]This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol:water(0.2 M sodium chloride) partition coefficient is 0.43.

Each tablet for oral administration contains venlafaxine hydrochloride equivalent to __ mg venlafaxine. In addition, each tablet contains the following inactive ingredients: [*Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance).]*

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or ∝-1 adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion. The relative bioavailability of venlafaxine from a tablet was 100% when compared to an oral solution. Food has no significant effect on the absorption of venlafaxine or on the formation of ODV.

The degree of binding of venlafaxine to human plasma is 27% ± 2% at concentrations ranging from 2.5 to 2215 ng/mL. The degree of ODV binding to human plasma is 30% ± 12% at concentrations ranging from 100 to 500 ng/mL. Protein-binding-induced drug interactions with venlafaxine are not expected.

Steady-state concentrations of both venlafaxine and ODV in plasma were attained within 3 days of multiple-dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 mg to 450 mg total dose per day (administered on a every 8 hour schedule). Plasma clearance, elimination half-life and steady-state volume of distribution were unaltered for both venlafaxine and ODV after multiple-dosing. Mean ± SD steady-state plasma clearance of venlafaxine and ODV is 1.3 ± 0.6 and 0.4 ± 0.2 L/h/kg, respectively; elimination half-life is 5 ± 2

and 11 ± 2 hours, respectively; and steady-state volume of distribution is 7.5 ± 3.7 L/kg and 5.7 ± 1.8 L/kg, respectively. When equal daily doses of venlafaxine were administered as either bid or tid regimens, the drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following both regimens.

Age and Gender
A pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both bid and tid regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered due to age or gender differences. Dosage adjustment based upon the age or gender of a patient is generally not necessary (see DOSAGE AND ADMINISTRATION).

Liver Disease
In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60% and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects.

Dosage adjustment is necessary in these patients (see DOSAGE AND ADMINISTRATION).

Renal Disease
In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR=10-70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR =10-70 mL/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56%, compared to normal subjects. A large degree of intersubject variability was noted.

Dosage adjustment is necessary in these patients (see DOSAGE AND ADMINISTRATION).

Clinical Trials

The efficacy of venlaxafine hydrochloride as a treatment for depression was established in 5 placebo-controlled, short-term trials. Four of these were 6 week trials in outpatients meeting DSM-III or DSM-III-R criteria for major depression: two involving dose titration with venlaxafine hydrochloride in a range of 75 to 225 mg/day (tid schedule), the third involving fixed venlaxafine doses of 75, 225, and 375 mg/day (tid schedule), and the fourth involving doses of 25, 75, and 200 mg/day (bid schedule). The fifth was a 4 week study of inpatients meeting DSM-III-R criteria for major depression with melancholia whose venlaxafine doses were titrated in a range of 150 to 375 mg/day (tid schedule). In these 5 studies, venlaxafine was shown to be significantly superior to placebo on at least 2 of the following 3 measures: Hamilton Depression Rating Scale (total score), Hamilton depressed mood item, and Clinical Global Impression-Severity of Illness rating. Doses from 75 to 225 mg/day were superior to placebo in outpatient studies and a mean dose of about 350 mg/day was effective in inpatients. Data from the 2 fixed-dose outpatient studies were suggestive of a dose-response relationship in the range of 75 to 225 mg/day. There was no suggestion of increased response with doses greater than 225 mg/day.

While there were no efficacy studies focusing specifically on an elderly population, elderly patients were included among the patients studied. Overall, approximately 2/3 of all patients in these trials were women. Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

INDICATIONS AND USAGE

Venlafaxine hydrochloride tablets are indicated for the treatment of depression.

The efficacy of venlaxafine hydrochloride in the treatment of depression was established in 6 week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III or DSM-III-R category of major depressive disorder and in a 4 week controlled trial of inpatients meeting diagnostic criteria for major depressive disorder with melancholia (see CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The effectiveness of venlaxafine hydrochloride in long-term use, that is, for more than 4 to 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use venlaxafine hydrochloride for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Venlafaxine hydrochloride is contraindicated in patients known to be hypersensitive to it.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).

WARNINGS

POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on venlafaxine hydrochloride, or who have recently had venlaxafine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with a monoamine oxidase inhibitor, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. Therefore, it is recommended that venlaxafine not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlaxafine, at least 7 days should be allowed after stopping venlaxafine before starting an MAOI.

Sustained Hypertension
Venlafaxine treatment is associated with sustained increases in blood pressure. (1) In a premarketing study comparing three fixed doses of venlafaxine (75, 225, and 375 mg/day) and placebo, a mean increase in supine diastolic blood pressure (SDBP) of 7.2 mm Hg was seen in the 375 mg/day group at week 6 compared to essentially no changes in the 75 and 225 mg/day groups and a mean decrease in SDBP of 2.2 mm Hg in the placebo group. (2) An analysis for patients meeting criteria for sustained hypertension (defined as treatment-emergent SDBP ≥ 90 mm Hg *and* ≥ 10 mm Hg above baseline for 3 consecutive visits) revealed a dose-dependent increase in the incidence of sustained hypertension for venlafaxine:

Probability of Sustained Elevation in SDBP (Pool of Premarketing Venlafaxine Studies)	
Treatment Group	**Incidence of Sustained Elevation in SDBP**
Venlafaxine	
<100 mg/day	3%
101-200 mg/day	5%
201-300 mg/day	7%
>300 mg/day	13%
Placebo	2%

An analysis of the patients with sustained hypertension and the 19 venlafaxine patients who were discontinued from treatment because of hypertension (<1% of total venlafaxine-treated group) revealed that most of the blood pressure increases were in a modest range (10 to 15 mm Hg, SDBP). Nevertheless, sustained increases of this magnitude could have adverse consequences. Therefore, it is recommended that patients receiving venlafaxine have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.

PRECAUTIONS

General
Anxiety and Insomnia
Treatment-emergent anxiety, nervousness, and insomnia were more commonly reported for venlafaxine-treated patients compared to placebo-treated patients in a pooled analysis of short-term, double-blind, placebo-controlled depression studies:

Venlafaxine Placebo

Symptom	n=1033	n=609
Anxiety	6%	3%
Nervousness	13%	6%
Insomnia	18%	10%

Anxiety, nervousness, and insomnia led to drug discontinuation in 2%, 2%, and 3%, respectively, of the patients treated with venlafaxine in the phase 2-3 depression studies.

Changes in Appetite and Weight
Treatment-emergent anorexia was more commonly reported for venlafaxine-treated (11%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled depression studies. A dose-dependent weight loss was often noted in patients treated with venlafaxine for several weeks. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of venlafaxine treatment. A loss of 5% or more of body weight occurred in 6% of patients treated with venlafaxine compared with 1% of patients treated with placebo and 3% of patients treated with another antidepressant. However, discontinuation for weight loss associated with venlafaxine was uncommon (0.1% of venlafaxine-treated patients in the phase 2-3 depression trials).

Activation of Mania/Hypomania
During phase 2-3 trials, hypomania or mania occurred in 0.5% of patients treated with venlafaxine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, venlafaxine should be used cautiously in patients with a history of mania.

Seizures
During premarketing testing, seizures were reported in 0.26% (8/3082) of venlafaxine-treated patients. Most seizures (5 of 8) occurred in patients receiving doses of 150 mg/day or less. Venlafaxine should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide
The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for venlafaxine hydrochloride should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness
Clinical experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering venlafaxine to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for 769 patients who received venlafaxine in 4 to 6 week double-blind placebo-controlled trials, however, showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo. The mean heart rate in venlafaxine-treated patients was increased relative to baseline by about 4 beats per minute.

In patients with renal impairment (GFR=10-70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolite were decreased, thus prolonging the elimination half-lives of these substances. A lower dose may be necessary (see DOSAGE AND ADMINISTRATION). Venlafaxine hydrochloride, like all antidepressants, should be used with caution in such patients.

Information For Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe venlafaxine hydrochloride tablets:

Interference with Cognitive and Motor Performance
Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that venlafaxine hydrochloride therapy does not adversely affect their ability to engage in such activities.

Pregnancy
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing
Patients should be advised to notify their physician if they are breast-feeding an infant.

Concomitant Medication
Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol
Although venlafaxine has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking venlafaxine.

Allergic Reactions
Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Laboratory Tests
There are no specific laboratory tests recommended.

Drug Interactions
As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Drugs Highly Bound to Plasma Protein
Venlafaxine is not highly bound to plasma proteins; therefore, administration of venlafaxine to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Lithium
The steady-state pharmacokinetics of venlafaxine administered as 50 mg every 8 hours were not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. O-desmethylvenlafaxine (ODV) was also unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium.

Diazepam
Under steady-state conditions for venlafaxine administered as 50 mg every 8 hours, a single 10 mg dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV in 18 healthy male subjects. Venlafaxine also did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam.

Administration of venlafaxine hydrochloride did not affect the psychomotor and psychometric effects induced by diazepam.

Cimetidine
Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs resulted in inhibition of first-pass metabolism of venlafaxine in 18 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, co-administration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than is venlafaxine. Consequently, the overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with pre-existing hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction associated with the concomitant use of venlafaxine hydrochloride and cimetidine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

Alcohol
A single dose of ethanol (0.5 g/kg) had no effect on the pharmacokinetics of venlafaxine or ODV when venlafaxine was administered as a 50 mg dose every 8 hours in 15 healthy male subjects. The administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ Metabolism
In vitro studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by cytochrome $P_{450}IID_6$, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between venlafaxine and drugs that inhibit cytochrome $P_{450}IID_6$ metabolism. Drug interactions that reduce the metabolism of venlafaxine to ODV could potentially increase the plasma concentrations of venlafaxine and lower the concentrations of the active metabolite.

Drugs Metabolized by Cytochrome $P_{450}IID_6$
In vitro studies indicate that venlafaxine is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. However, the clinical significance of this finding is unknown.

Monoamine Oxidase Inhibitors
See CONTRAINDICATIONS and WARNINGS.

CNS-Active Drugs
The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated (except in the case of lithium and diazepam, as noted above). Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required.

Electroconvulsive Therapy
There are no clinical data establishing the benefit of electroconvulsive therapy combined with venlafaxine treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Venlafaxine was given by oral gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 16 times, on a mg/kg basis, and 1.7 times on a mg/m^2 basis, the maximum recommended human dose. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma levels of venlafaxine were 1 times (male rats) and 6 times (female rats) the plasma levels of patients receiving the maximum recommended human dose. Plasma levels of the O-desmethyl metabolite were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenicity
Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic in the *in vitro* BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured CHO cells, or the *in vivo* chromosomal aberration assay in rat bone marrow. ODV was not mutagenic in the *in vitro* CHO cell chromosomal aberration assay. There was a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow in male rats receiving 200 times, on a mg/kg basis, or 50 times, on a mg/m^2 basis, the maximum human daily dose. The no effect dose was 67 times (mg/kg) or 17 times (mg/m^2) the human dose.

Impairment of Fertility
Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 8 times the maximum recommended human daily dose on a mg/kg basis, or up to 2 times on a mg/m^2 basis.

Pregnancy
Teratogenic Effects: Pregnancy Category C
Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 11 times (rat) or 12 times (rabbit) the maximum recommended human daily dose on a mg/kg basis, or 2.5 times (rat) and 4 times (rabbit) the human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 10 times (mg/kg) or 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 1.4 times the human dose on a mg/kg basis or 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal

reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery
The effect of venlafaxine hydrochloride on labor and delivery in humans is unknown.

Nursing Mothers
It is not known whether venlafaxine hydrochloride or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when venlafaxine is administered to a nursing woman.

Usage in Children
Safety and effectiveness in individuals below 18 years of age have not been established.

Geriatric Use
Of the 2,897 patients in phase 2-3 depression studies with venlafaxine, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment
Nineteen percent (537/2897) of venlafaxine patients in phase 2-3 depression studies discontinued treatment due to an adverse event. The more common events (≥1%) associated with discontinuation and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for venlafaxine compared to placebo) included:

	Venlafaxine	Placebo
CNS		
Somnolence	3%	1%
Insomnia	3%	1%
Dizziness	3%	--
Nervousness	2%	--
Dry mouth	2%	--
Anxiety	2%	1%
GASTROINTESTINAL		
Nausea	6%	1%
UROGENITAL		

Abnormal ejaculation*		3%		--
OTHER				
Headache		3%		1%
Asthenia	2%		--	
Sweating	2%		--	

* Percentages based on the number of males.
-- Less than 1%

Incidence in Controlled Trials

Commonly Observed Adverse Events In Controlled Clinical Trials

The most commonly observed adverse events associated with the use of venlafaxine (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (i.e., incidence for venlafaxine at least twice that for placebo), derived from the 1% incidence table below, were asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence in men.

Adverse Events Occurring at an Incidence of 1% or More Among Venlafaxine-Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among venlafaxine-treated patients who participated in short-term (4 week to 8 week) placebo-controlled trials in which patients were administered doses in a range of 75 to 375 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

TABLE 1.
Treatment-Emergent Adverse Experience Incidence in 4 Week to 8 Week Placebo-Controlled Clinical Trials[1]

Body System	Preferred Term	Venlafaxine (N=1033)	Placebo (N=609)
Body as a Whole	Headache	25%	24%
	Asthenia	12%	6%
	Infection	6%	5%
	Chills	3%	--
	Chest pain	2%	1%
	Trauma	2%	1%
Cardiovascular	Vasodilatation	4%	3%
	Increased blood pressure/hypertension	2%	--
	Tachycardia	2%	--
	Postural hypotension	1%	--
Dermatological	Sweating	12%	3%
	Rash	3%	2%
	Pruritus	1%	--
Gastrointestinal	Nausea	37%	11%
	Constipation	15%	7%
	Anorexia	11%	2%
	Diarrhea	8%	7%
	Vomiting	6%	2%
	Dyspepsia	5%	4%
	Flatulence	3%	2%
Metabolic	Weight loss	1%	--

Nervous System	Somnolence	23%	9%
	Dry mouth	22%	11%
	Dizziness	19%	7%
	Insomnia	18%	10%
	Nervousness	13%	6%
	Anxiety	6%	3%
	Tremor	5%	1%
	Abnormal dreams	4%	3%
	Hypertonia	3%	2%
	Paresthesia	3%	2%
	Libido decreased	2%	--
	Agitation	2%	--
	Confusion	2%	1%
	Thinking abnormal	2%	1%
	Depersonalization	1%	--
	Depression	1%	--
	Urinary retention	1%	--
	Twitching	1%	--
Respiration	Yawn	3%	--
Special Senses	Blurred vision	6%	2%
	Taste perversion	2%	--
	Tinnitus	2%	--
	Mydriasis	2%	--
Urogenital System	Abnormal ejaculation/orgasm	12%[2]	--[2]
	Impotence	6%[2]	--[2]
	Urinary frequency	3%	2%
	Urination impaired	2%	--
	Orgasm disturbance	2%[3]	--[3]
	Menstrual disorder	1%[3]	--[3]

[1] Events reported by at least 1% of patients treated with venlafaxine hydrochloride) are included, and are rounded to the nearest %. Events for which the venlafaxine incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, pain, back pain, flu syndrome, fever, palpitation, increased appetite, myalgia, arthralgia, amnesia, hypesthesia, rhinitis, pharyngitis, sinusitis, cough increased, urinary tract infection, and dysmenorrhea[(3)].

-- Incidence less than 1%.

[2] Incidence based on number of male patients.

[3] Incidence based on number of female patients.

Dose Dependency Of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing venlafaxine hydrochloride 75, 225, and 375 mg/day with placebo revealed a dose dependency for some of the more common adverse events associated with venlafaxine use, as shown in the table that follows. The rule for including events was to enumerate those that occurred at an incidence of 5% or more for at least one of the venlafaxine groups and for which the incidence was at least twice the placebo incidence for at least one venlafaxine group. Tests for potential dose relationships for these events (Cochran- Armitage Test, with a criterion of exact 2-sided p-value ≤ 0.05) suggested a dose-dependency for several adverse events in this list, including chills, hypertension, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation.

TABLE 2.
Treatment-Emergent Adverse Experience Incidence In a Dose Comparison Trial

Body System/ Preferred Term	**Placebo (N=92)**	**Venlafaxine Hydrochloride (mg/day) 75 (N=89)**	**225 (N=89)**	**375 (N=88)**
Body as a Whole				
Abdominal pain	3.3%	3.4%	2.2%	8.0%
Asthenia	3.3%	16.9%	14.6%	14.8%
Chills	1.1%	2.2%	5.6%	6.8%
Infection	2.2%	2.2%	5.6%	2.3%
Cardiovascular System				
Hypertension	1.1%	1.1%	2.2%	4.5%
Vasodilatation	0.0%	4.5%	5.6%	2.3%
Digestive System				
Anorexia	2.2%	14.6%	13.5%	17.0%
Dyspepsia	2.2%	6.7%	6.7%	4.5%
Nausea	14.1%	32.6%	38.2%	58.0%
Vomiting	1.1%	7.9%	3.4%	6.8%
Nervous System				
Agitation	0.0%	1.1%	2.2%	4.5%
Anxiety	4.3%	11.2%	4.5%	2.3%
Dizziness	4.3%	19.1%	22.5%	23.9%
Insomnia	9.8%	22.5%	20.2%	13.6%
Libido decreased	1.1%	2.2%	1.1%	5.7%
Nervousness	4.3%	21.3%	13.5%	12.5%
Somnolence	4.3%	16.9%	18.0%	26.1%
Tremor	0.0%	1.1%	2.2%	10.2%

Respiratory System				
Yawn	0.0%	4.5%	5.6%	8.0%
Skin and Appendages				
Sweating	5.4%	6.7%	12.4%	19.3%
Special Senses				
Abnormality of accommodation	0.0%	9.1%	7.9%	5.6%
Urogenital System				
Abnormal ejaculation/orgasm	0.0%	4.5%	2.2%	12.5%
Impotence	0.0%	5.8%	2.1%	3.6%
(Number of men)	(n=63)	(n=52)	(n=48)	(n=56)

Adaptation to Certain Adverse Events
Over a 6 week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., dizziness and nausea), but less to other effects (e.g., abnormal ejaculation and dry mouth).

Vital Sign Changes
Venlafaxine hydrochloride treatment (averaged over all dose groups) in clinical trials was associated with a mean increase in pulse rate of approximately 3 beats per minute, compared to no change for placebo. It was associated with mean increases in diastolic blood pressure ranging from 0.7 to 2.5 mm Hg averaged over all dose groups, compared to mean decreases ranging from 0.9 to 3.8 mm Hg for placebo. However, there is a dose dependency for blood pressure increase (see WARNINGS).

Laboratory Changes
Of the serum chemistry and hematology parameters monitored during clinical trials with venlafaxine, a statistically significant difference with placebo was seen only for serum cholesterol, i.e., patients treated with venlafaxine had mean increases from baseline of 3 mg/dL, a change of unknown clinical significance.

ECG Changes
In an analysis of ECGs obtained in 769 patients treated with venlafaxine and 450 patients treated with placebo in controlled clinical trials, the only statistically significant difference observed was for heart rate, i.e., a mean increase from baseline of 4 beats per minute for venlafaxine.

Other Events Observed During the Premarketing Evaluation of Venlafaxine
During its premarketing assessment, multiple doses of venlafaxine were administered to 2181 patients in phase 2 and 3 studies. The conditions and duration of exposure to venlafaxine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2181 patients exposed to multiple doses of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Table 1 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine hydrochloride, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Frequent*: accidental injury, malaise, neck pain; *Infrequent*: abdomen enlarged, allergic reaction, cyst, face edema, generalized edema, hangover effect, hernia, intentional injury, moniliasis, neck rigidity, overdose, chest pain substernal, pelvic pain, photosensitivity reaction, suicide attempt; *Rare*: appendicitis, body odor, carcinoma, cellulitis, halitosis, ulcer, withdrawal syndrome.

Cardiovascular System: *Frequent*: migraine; *Infrequent*: angina pectoris, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; *Rare*: arrhythmia, first-degree atrioventricular block, bradycardia, bundle branch block, mitral valve disorder, mucocutaneous hemorrhage, sinus bradycardia, varicose vein.

Digestive System: *Frequent*: dysphagia, eructation; *Infrequent*: colitis, tongue edema, esophagitis, gastritis, gastroenteritis, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, stomatitis, stomach ulcer, mouth ulceration; *Rare*: cheilitis, cholecystitis, cholelithiasis, hematemesis, gum hemorrhage, hepatitis, ileitis, jaundice, oral moniliasis, intestinal obstruction, proctitis, increased salivation, soft stools, tongue discoloration, esophageal ulcer, peptic ulcer syndrome.

Endocrine System: *Rare*: goiter, hyperthyroidism, hypothyroidism.

Hemic and Lymphatic System: *Frequent*: ecchymosis; *Infrequent*: anemia, leukocytosis, leukopenia, lymphadenopathy, lymphocytosis, thrombocythemia, thrombocytopenia, WBC abnormal; *Rare*: basophilia, cyanosis, eosinophilia, erythrocytes abnormal.

Metabolic and Nutritional: *Frequent*: peripheral edema, weight gain; *Infrequent*: alkaline phosphatase increased, creatinine increased, diabetes mellitus, edema, glycosuria, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, SGOT increased, thirst; *Rare*: alcohol intolerance, bilirubinemia, BUN increased, gout, hemochromatosis, hyperkalemia, hyperphosphatemia, hypoglycemic reaction, hyponatremia, hypophosphatemia, hypoproteinemia, SGPT increased, uremia.

Musculoskeletal System: *Infrequent*: arthritis, arthrosis, bone pain, bone spurs, bursitis, joint disorder, myasthenia, tenosynovitis; *Rare*: osteoporosis.

Nervous System: *Frequent*: emotional lability, trismus, vertigo; *Infrequent*: apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypertonia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, paranoid reaction, psychosis, psychotic depression, sleep disturbance, abnormal speech, stupor, torticollis; *Rare*: akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, hypokinesia, neuritis, nystagmus, reflexes increased, seizures.

Respiratory System: *Frequent*: bronchitis, dyspnea; *Infrequent*: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; *Rare*: atelectasis, hemoptysis, hypoxia, pleurisy, pulmonary embolus, sleep apnea, sputum increased.

Skin and Appendages: *Infrequent*: acne, alopecia, brittle nails, contact dermatitis, dry skin, herpes simplex, herpes zoster, maculopapular rash, urticaria; *Rare*: skin atrophy, exfoliative dermatitis, fungal dermatitis, lichenoid dermatitis, hair discoloration, eczema, furunculosis, hirsutism, skin hypertrophy, leukoderma, psoriasis, pustular rash, vesiculobullous rash.

Special Senses: *Frequent*: abnormal vision, ear pain; *Infrequent*: cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, otitis media, parosmia, photophobia, subconjunctival hemorrhage, taste loss, visual field defect; *Rare*: blepharitis, chromatopsia, conjunctival edema, deafness, glaucoma, hyperacusis, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, scleritis.

Urogenital System: *Frequent*: anorgasmia, dysuria, hematuria, metrorrhagia*, urination impaired, vaginitis*; *Infrequent*: albuminuria, amenorrhea*, kidney calculus, cystitis, leukorrhea, menorrhagia*, nocturia, bladder pain, breast pain, kidney pain, polyuria, prostatitis*, pyelonephritis, pyuria, urinary incontinence, urinary urgency, uterine fibroids enlarged*, uterine hemorrhage*, vaginal hemorrhage*, vaginal moniliasis*, *Rare*: abortion*, breast engorgement, breast enlargement, calcium crystalluria, female lactation*, hypomenorrhea*, menopause*, prolonged erection*, uterine spasm*.

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* Based on the number of male or female patients as appropriate.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Venlafaxine hydrochloride is not a controlled substance.

Physical and Psychological Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

While the discontinuation effects of venlafaxine have not been systematically evaluated in controlled clinical trials, a retrospective survey of new events occurring during taper or following discontinuation revealed the following six events that occurred at an incidence of at least 5% and for which the incidence for venlafaxine was at least twice the placebo incidence: asthenia, dizziness, headache, insomnia, nausea, and nervousness. Therefore, it is recommended that the dosage be tapered gradually and the patient monitored (see DOSAGE AND ADMINISTRATION).

While venlafaxine has not been systematically studied in clinical trials for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There were 14 reports of acute overdose with venlafaxine hydrochloride, either alone or in combination with other drugs and/or alcohol, among the patients included in the premarketing evaluation. The majority of the reports involved ingestions in which the total dose of venlafaxine taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g, and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 mcg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 mcg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients

reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

In postmarketing experience, venlafaxine, taken alone, has not been clearly associated with lethal overdose. However, fatal reactions have been reported in patients taking overdoses of venlafaxine in combination with alcohol and/or other drugs.

Overdosage Management
Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitoring of cardiac rhythm and vital signs is recommended. General supportive and symptomatic measures are also recommended. Use of activated charcoal, induction of emesis, or gastric lavage should be considered. Due to the large volume of distribution of venlafaxine hydrochloride, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine hydrochloride are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Initial Treatment
The recommended starting dose for venlafaxine hydrochloride tablets is 75 mg/day, administered in two or three divided doses, taken with food. Depending on tolerability and the need for further clinical effect, the dose may be increased to 150 mg/day. If needed, the dose should be further increased up to 225 mg/day. When increasing the dose, increments of up to 75 mg/day should be made at intervals of no less than 4 days. In outpatient settings there was no evidence of usefulness of doses greater than 225 mg/day for moderately depressed patients, but more severely depressed inpatients responded to a mean dose of 350 mg/day. Certain patients, including more severely depressed patients, may therefore respond more to higher doses, up to a maximum of 375 mg/day, generally in three divided doses.

Dosage for Patients with Hepatic Impairment
Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared to normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by 50% in patients with moderate hepatic impairment. Since there was much individual variability in clearance between patients with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Dosage for Patients with Renal Impairment
Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR=10-70 mL/min) compared to normals (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by 25% in patients with mild to moderate renal impairment. It is recommended that the total daily dose be reduced by 50% and the dose be withheld until the dialysis treatment is completed (4 hrs) in patients undergoing hemodialysis. Since there was much individual variability in clearance between patients with renal impairment, individualization of dosing may be desirable in some patients.

Dosage for Elderly Patients
No dose adjustment is recommended for elderly patients on the basis of age. As with any antidepressant, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance/Continuation/Extended Treatment
There is no body of evidence available to answer the question of how long a patient should continue to be treated with venlafaxine. It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Discontinuing Venlafaxine Hydrochloride
When discontinuing venlafaxine after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms. Patients who have received venlafaxine for 6 weeks or more should have their dose tapered gradually over a 2 week period.

Switching Patients to or from a Monoamine Oxidase Inhibitor
At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with venlafaxine hydrochloride. In addition, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

HOW SUPPLIED

- Established Name
- Strength of dosage form
- Packaging, NDC number
- Dosage form, shape, color, scoring, imprinting
  Note: All strengths of the innovator's tablets are scored.
- Store at controlled room temperature, 15°C to 30°C (59°C to 86°C), in a dry place.
- Dispense in a well-closed container as defined in the USP.
- "Caution: Federal Law..." statement.

Include the following information at the end of the HOW SUPPLIED section:

- Date of latest revision.
- "Manufactured by" statement. - Should be consistent with container labels and/or carton labeling.

CONTAINER LABEL

In addition to the general label requirements ("Caution: Federal Law..." statement, statement of net quantity, etc.) please include the following:

Main Panel:

- The established name and strength should read as follows:

  VENLAFAXINE HYDROCHLORIDE TABLETS

  __ mg*
- If manufacturing multiple strengths, we encourage you to differentiate your product strengths by boxing, contrasting colors or some other means.

Side Panel:

- Each tablet contains statement should read as follows:

  *Each tablet contains venlafaxine hydrochloride equivalent to __ mg venlafaxine.

- Usual Dosage: See package insert.
- Store at controlled room temperature 15° to 30°C (59° to 86°F), in a dry place.
- Dispense in a well-closed container, as defined in the USP.